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PREPARATION, CHARACTERIZATION AND EVALUATION OF PGS - PVP CO-PROCESSED EXCIPIENT AS DIRECTLY COMPRESSIBLE VEHICLE IN TABLET FORMULATION

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ABSTRACT

Direct compression is the preferred method for the preparation of tablets. Co-processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible vehicles. The objective of the present study is to prepare and characterize pregelatinized starch-poly vinyl pyrrolidone (PGS-PVP) co-processed excipient and to evaluate its application as directly compressible vehicle in tablet formulations. PGS-PVP co-processed excipient was prepared by gelatinizing potato starch in the presence of PVP and drying the resulting mass. The co-processed excipient prepared was characterized by determining melting point, solubility, swelling index in water, pH, and micromeritic characters namely particle size, bulk density, tapped density, angle of repose and compressibility index, by FTIR spectra and evaluated for its application in tablet formulations. PGS-PVP co-processed excipient prepared by gelatinizing potato starch (49 parts) in the presence of PVP (1 part) is a crystalline, discrete and free flowing powder. It is insoluble in water and aqueous fluids of pH 1.2, 4.5 and 7.4 and in several organic solvents. It exhibited high swelling (284 %) in water. PGS-PVP co-processed excipient has excellent flow properties alone and as blends with selected drugs it exhibited excellent to good flow properties. Tablets of (i) sulphamethoxazole (ii) paracetamol and (iii) aceclofenac prepared by direct compression method employing PGS-PVP co-processed excipient as DCV were of good quality with regard to drug content, hardness, friability and disintegration time. All the tablets formulated disintegrating rapidly within 3.5 min. With all the three drugs, the tablets prepared gave rapid dissolution of the contained drug, 100 % within 20 min and fulfilled the official (IP/USP) dissolution rate test specification prescribed in each case. FTIR spectra indicated no interaction between PGS-PVP co-processed excipient and the three drugs included in the study. Thus, PGS-PVP co-processed excipient developed in this study was found to be a promising directly compressible vehicle for the preparation of tablets.

INTRODUCTION: Direct compression is the preferred method for the preparation of tablets [1]. It offers several advantages [2-3]. Notable among them are (i) It is economical compared to wet granulation since it requires fewer unit operations (ii) More suitable for moisture and heat sensitive APIs since it eliminates wetting and drying steps (iii) Changes in dissolution profile are less likely to occur in tablets made by direct

compression method on storage than in those made from granulations [4]. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms [5]. Disintegration or dissolution is the rate limiting step in absorption in the case of tablets of poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution.

The direct compression process is mainly influenced by the properties of the excipients. The physico mechanical properties of excipients that ensure a robust and successful process are good flowability, good compressibility, low or no moisture sensitivity, low lubricant sensitivity, and good machineability even in high-speed tabletting machinery with reduced dwell times [6].

The majority of the excipients that are currently available fail to give up to these functionality requirements, thus creating the opportunity for the development of new high-functionality excipients. An efficient platform for the manipulation of excipient functionality is provided by co-processing two or more existing excipients. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients [7].

The availability of a large number of excipients for co-processing ensures numerous possibilities to produce tailor-made “designer excipients” to address specific functionality requirements. Co-processed excipients are prepared by incorporating one excipient into the particle structure of another excipient using processes such as co-drying.

Co-processing of excipients in the pharmaceutical industry can be dated back to the late 1980’s with the introduction of co-processed microcrystalline cellulose and calcium carbonate[8], followed by Cellactose (Meggle Corp.,Wasserburg, Germany) in 1990, which is a co-processed combination of cellulose and lactose.

A similar principle was applied in developing silicified microcrystalline cellulose (SPVP), which is the most widely used co-processed excipient [9].

The objective of the present study is to prepare and characterize pregelatinized starch-polyvinylpyrrolidone (PGS-PVP) co-processed excipient and to evaluate its application as directly compressible vehicle in tablet formulations. PGS-PVP co- processed excipeint was prepared by gelatinizing potato starch in the presence of PVP and drying the resulting mass.

EXPERIMENTAL:

Materials: Sulphamethoxazole, paracetamol and aceclofenac were gift samples from M/s Natco Pharma Ltd. Hyderabad. Poly vinyl pyrrolidone (PVP) was a gift sample from M/s Eisai Pharmatechnology and Manufacturing Pvt. Ltd., Visakhapatnam. Potato starch, lactose, talc and magnesium stearate were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Methods:

Preparation of PGS-PVP Co-processed Excipient: Potato starch (49 parts) and poly vinyl pyrrolidone (1 part) were dispersed in 20 parts of water to form a smooth slurry. Purified water (40 parts) was taken in a separate beaker and heated to boiling. Starch - PVP slurry was added to boiling water while stirring. Stirring while heating was continued for 15 to 20 minutes to form a thick mass. The product formed was collected on to stainless steel tray and dried at 80^{o}C for 12 hours. The dried product was grinded and sized to obtain -72+100 mesh sized particles.

Characterization of PGS-PVP Co-processed Excipient: PGS-PVP co-processed excipient prepared was characterized by determining melting point, solubility, swelling index in water, pH, and micromeritic characters namely particle size, bulk density, tapped density, angle of repose and compressibility index and by FTIR spectra.

Solubility: Solubility of PGS-PVP was tested in water, aqueous buffers of pH 1.2, 4.5, and 7.4 and organic solvents such as alcohol, dichloromethane, chloroform, acetone and petroleum ether.

pH: The pH of a 1% w/v slurry was measured.

Melting point: Melting point was determined by using melting point apparatus.

Swelling Index [10]: PGS-PVP (500 mg) was added to 10 ml of water and light paraffin taken in two different graduated test tubes and mixed. The dispersion in the tubes was allowed to stand for 24 hrs. The volumes of the sediment in the tubes were recorded. The Swelling index of the material was calculated as follows.

S.I. (%) = (Volume of sediment in water – Volume of sediment in light liquid paraffin)/ (Volume of sediment in liquid paraffin)

Particle size: Particle size analysis was done by sieving using standard sieves.

Bulk density [11]: Bulk density (g/cc) was determined by three tap method in graduated cylinder.

Angle of repose [12]: Angle of repose was measured by fixed funnel method.

Compressibility index [13]: Compressibility index (CI) was determined by measuring the initial volume (V_0) and final volume (V) after hundred tappings of a sample of the product in a measuring cylinder.

CI was calculated using equation,

$$\text{Compressibility index (CI)} = [(V_0\text{-}V)/V_0] \times 100$$

Preparation of Tablets by Direct Compression Method: Tablets of (i) Sulphamethoxazole (100 mg) (ii) Paracetamol (100 mg) and Aceclofenac (100 mg) were prepared by direct compression method as per the formula given in the Table 2. All the materials required as per the formula were blended in a closed polyethylene bag. The blends were compressed into tablets on a tablet punching machine (M/s Cadmach Machinery Co. Pvt. Ltd.,) to a hardness of 6 kg/cm^2 using 9 mm flat punches.

Evaluation of Tablets: All the tablets prepared were evaluated for content of active ingredient, hardness, friability, disintegration time and dissolution rate. Hardness of tablets was tested using Monsanto hardness tester. Friability of the tablets was determined in a Roche Friabilator. Disintegration time was determined in a Lab India tablet disintegration test machine (model: DT 1000) using water as test fluid.

Estimation of Drug Content in the Tablets: From each batch of tablets prepared 20 tablets were accurately weighed and powdered. Tablet powder equivalent to 50 mg of drug was taken for assay into a 100 ml conical flask and extracted with 3×20 ml quantities of methanol. The methanolic extracts were filtered and collected into a 100 ml volumetric flask and the volume was then made upto 100 ml with methanol. The solution was then suitably diluted with 0.1 N hydrochloric acid in the case of sulphamethoxazole, phosphate buffer of pH 5.8 in the case of paracetamol and phosphate buffer of pH 7.4 in the case of aceclofenac. The absorbance of the solutions was measured at 265 nm in the case of sulphamethoxazole, at 243 nm in the case of paracetamol and at 274 nm in the case of aceclofenac.

Dissolution Rate Study: Dissolution rate of the tablets prepared was studied employing USP 8 station Dissolution Rate Test Apparatus (M/s labindia Disso 8000) with a paddle stirrer at 50 rpm. Hydrochloric acid, 0.1N (900 ml), phosphate buffer of pH 5.8 (900 ml) and phosphate buffer of pH 7.4 (900 ml) were used as dissolution fluids for sulphamethoxazole, paracetamol and aceclofenac respectively. One tablet was used in each test. A temperature 37 ± 1^0C was maintained throughout. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45 µ) at different time intervals and assayed for sulphamethoxazole at 265 nm, paracetamol at 243 nm and aceclofenac at 274 nm. All the dissolution experiments were conducted in triplicate (n=3).

FTIR Spectra: FTIR spectra of the three pure drugs included in the study and their dispersions in PGS-PVP co-processed excipient were obtained with FTIR Spectrophotometer (Bruker ATR Alpha – e, Germany) in KBr disc.

RESULTS AND DISCUSSION: Directly compressible vehicles can be prepared by various methods [14-16]. Co-processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible vehicles. Co-processing of excipients could lead to the formation of excipients with superior properties compared to the simple physical mixtures of their components.

The objective of the present study is to prepare and characterize pregelatinized starch-poly vinyl pyrrolidone (PGS-PVP) co-processed excipient and to evaluate its application as directly compressible vehicle in tablet formulations.

PGS-PVP co-processed excipient was prepared by gelatinizing potato starch (49 parts) in the presence of PVP (1 part). The prepared PGS-PVP co-processed excipient was characterised by determining various physical and micromeritic properties. The PGS-PVP co-processed excipient prepared was found to be crystalline, discrete and free flowing powder. It could be ground to various particle sizes by grinding in a dry mortar. Particles of size -72+100 mesh (179.5 µm) were collected and used for further studies. The physical and micromeritic properties of PGS-PVP co-processed excipient prepared are summarised in **Table 1**.

TABLE 1: PHYSICAL AND MICROMERITIC PROPERTIES OF PGS-PVP CO-PROCESSED EXCIPIENT

Property/Test	Result
Melting point	Charred at 250^{0}C
Solubility	Insoluble in water, methanol, alcohol, acetone, chloroform, dichloro-methane and petroleum ether
Swelling Index (%)	High swelling in water; Swelling index 284 %
pH (1% aqueous dispersion)	6.8
Particle size (µm)	72/100 mesh (179.5 µm)
Bulk density (g/cc)	0.436
Tapped density (g/cc)	0.464
Angle of repose (^{o})	24.40
Compressibility index (%)	7.8

The PGS-PVP co-processed excipient prepared was charred at 250^{0}C.It is insoluble in water and aqueous fluids of pH 1.2, 4.5 and 7.4 and also in several organic solvents such as alcohol, methanol, dichloromethane, acetone, chloroform and petroleum ether. It exhibited high swelling in water and the swelling index was found to be 284 %.

The flow properties of the PGS-PVP co-processed excipient prepared were determined by measuring bulk density, angle of repose and compressibility index. The results given in Table 1 indicated that the excipient prepared has excellent flow properties. Directly compressible vehicles should be free flowing.

Flowability is required in order ensure homogeneous and rapid flow of powder for uniform die filling. During the short dwell-time (milliseconds), the required amount of powder blend should be transferred into die cavities with reproducibility of ±5%. As the PGS-PVP co-processed excipient possesses excellent flow properties, it is considered as a promising directly compressible vehicle for direct compression of tablets. Blends of PGS-PVP co-processed excipient and selected drugs (sulphamethoxazole, paracetamol and aceclofenac) also exhibited excellent to good flow properties. The estimated bulk density values of PGS-PVP co-processed excipient would also contribute to its good flow.

To evaluate the PGS-PVP co-processed excipient as directly compressible vehicle (DCV), tablets of (i) sulphamethoxazole (ii) paracetamol and (iii) aceclofenac were prepared by direct compression method employing PGS-PVP co-processed excipient as DCV at a strength of 60% in the formula. The tablets were prepared as per the formulae given **Table 2**. All the tablets prepared were evaluated for content of active ingredient, hardness, friability, and disintegration time and dissolution rate. The results are given in **Table 3**.

Hardness of the tablets was in the range 4.0 - 5.0 Kg/sq.cm. Weight loss in the friability test was in the range 1.45 – 2.10%.The drug content of the tablets was within 100 ± 3% of the labelled claim. All the tablets formulated disintegrating rapidly within 3.5 min. As such all the tablets prepared employing the PGS-PVP co-processed excipient were of good quality with regard to drug content, hardness, friability and disintegration time.

The results of the dissolution rate study are given in **Table 4**. With all the three drugs, the tablets prepared gave rapid dissolution of the contained drug. The dissolution was complete (100 %) within 20 min and fulfilled the official (IP/USP) dissolution rate test specification prescribed in each case.

The compatibility of the PGS-PVP co-processed excipient with the three drugs included in the study was evaluated by FTIR spectra. The FTIR spectra of pure drugs and their dispersions in PGS-PVP (1:1) are shown in **Fig. 1**.

TABLE 2: FORMULAE OF TABLETS PREPARED BY DIRECT COMPRESSION METHOD EMPLOYING PGS-PVP CO- PROCESSED EXCIPIENT

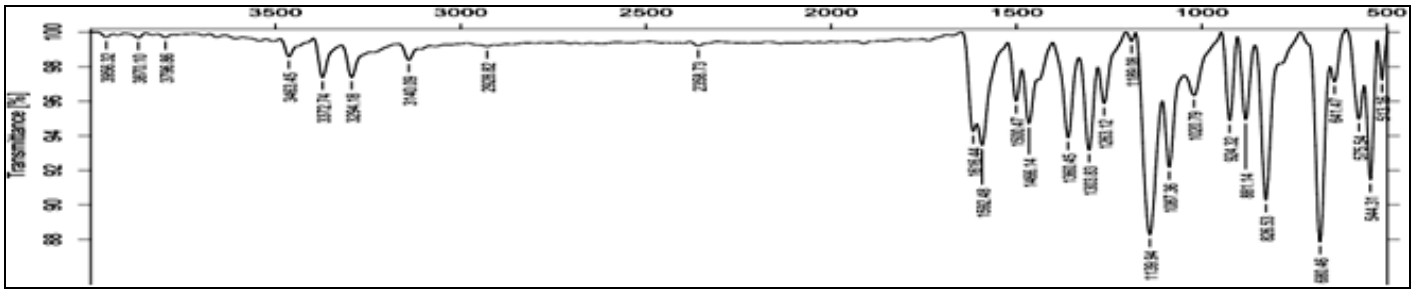
Ingredient (mg/tablet)	Tablet Formulation		
	Sulphamethoxazole	Paracetamol	Aceclofenac
Sulphamethoxazole	100	-	-
Paracetamol	-	100	-
Aceclofenac	-	-	100
PGS-PVP Co-processed excipient (72/100 mesh)	264	264	264
Lactose	58.4	58.4	58.4
Talc	8.8	8.8	8.8
Magnesium stearate	8.8	8.8	8.8
Tablet weight (mg)	440	440	440

TABLE 3: PHYSICAL PROPERTIES OF VARIOUS TABLETS PREPARED BY DIRECT COMPRESSION METHOD EMPLOYING PGS-PVP CO-PROCESSED EXCIPIENT

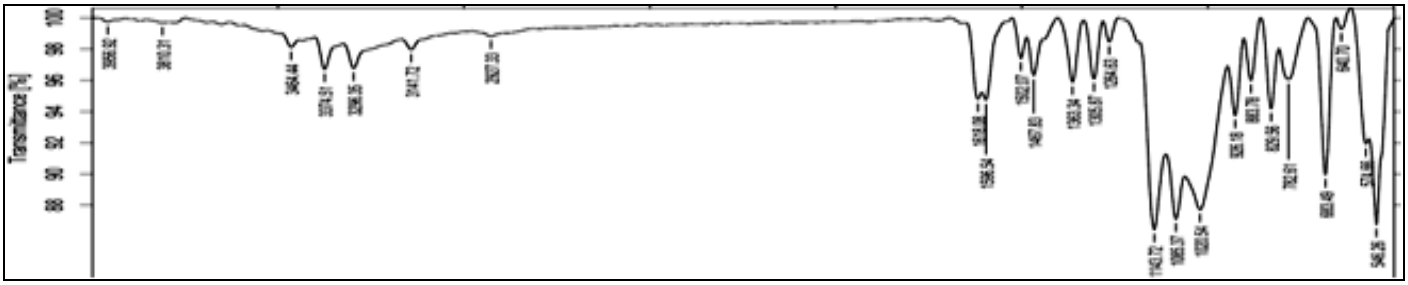
Formulation	Hardness (kg/sq.cm)	Friability (% weight loss)	Disintegration time (min-sec)	Drug content (mg/tablet)
Sulphamethoxazole tablets	4.0	1.45	3-00	98.5
Paracetamol tablets	5.0	2.10	3-15	99.2
Aceclofenac tablets	5.0	1.95	3-20	101.6

TABLE 4: DISSOLUTION RATE OF VARIOUS TABLETS FORMULATED BY DIRECT COMPRESSION METHOD EMPLOYING PGS-PVP CO-PROCESSED EXCIPIENT PREPARED

Formulation	Percent Drug Dissolved (%) at Time (min)				Official Dissolution Rate Specification
	5	10	15	20	
Sulphamethoxazole tablets	64.80	88.50	97.20	100	NLT 80 % in 30 min. (USP 2010)
Paracetamol tablets	72.60	98.80	99.90	100	NLT 80 % in 30 min. (USP 2010)
Aceclofenac tablets	81.42	100	100	100	NLT 75% in 45 min. (IP 2010)

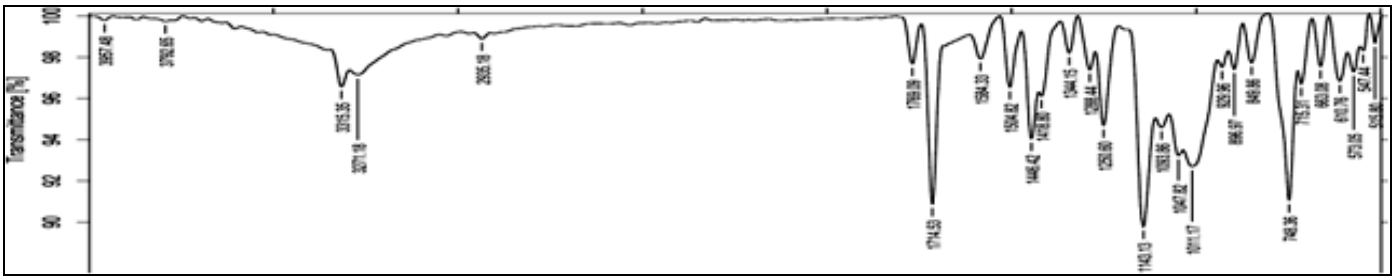


SULPHAMETHOXAZOLE

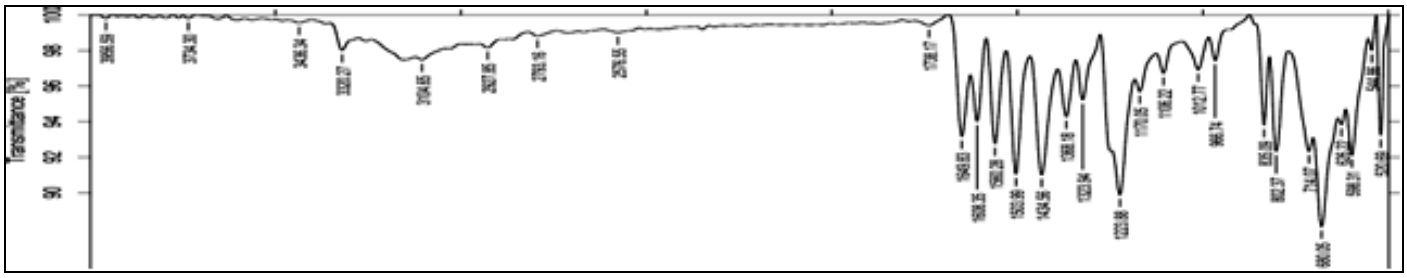


SULPHAMETHOXAZOLE- DCV

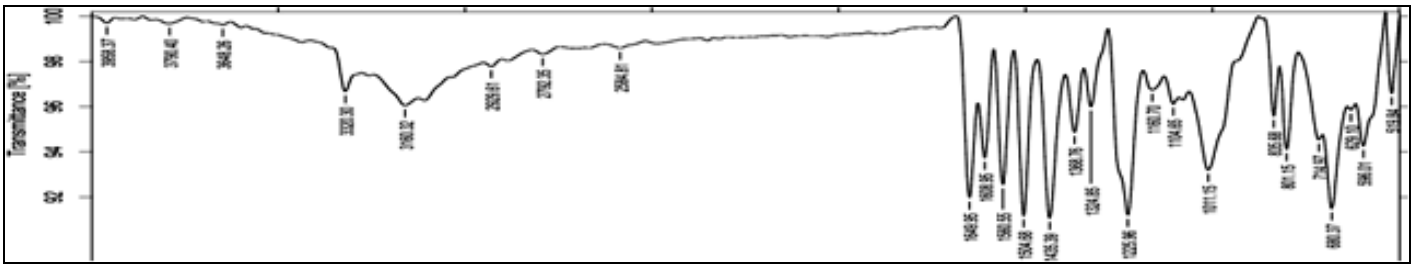
ACECLOFENAC



ACECLOFENAC- DCV



PARACETAMOL



PARACETAMOL- DCV

FIG. 1: FTIR SPECTRA OF PURE DRUGS AND THEIR DISPERSIONS IN PGS-PVP CO-PROCESSED EXCIPIENT

The FTIR spectra of pure drugs and the dispersions of drug in PGS-PVP excipient (1:1) were identical in each case indicating no interaction between the PGS-PVP co-processed excipient and the three drugs included in the study.

The FTIR spectra of both sulphamethoxazole pure drug and its dispersions in PGS-PVP showed the characteristic peaks of sulphamethoxazole at 3463 cm^{-1} and 3372 cm^{-1} due to antisymmetric and symmetric stretching vibrations of aniline NH_2 group respectively, at 3294 cm^{-1} due to sulphonamide NH, at 1592 -1596 cm^{-1} due to C=C stretching of phenyl ring, at 1467 cm^{-1} due to isoxazole ring vibrations and at 1305 - 1316 cm^{-1} and 1140 cm^{-1} due to antisymmetric and symmetric SO_2 vibrations.

The FTIR spectra of both aceclofenac pure drug and its dispersions in PGS-PVP showed the characteristic peaks of aceclofenac at 849 cm^{-1} due to C-Cl stretching, at 1712 cm^{-1}, 3314 cm^{-1} respectively due to C=O and O-H stretching of COOH functional group. The FTIR spectra of both paracetamol pure drug and its dispersions in PGS-PVP showed the characteristic peaks of paracetamol at 3320 cm^{-1} and 3160 cm^{-1} due to OH groups, at 1649 cm^{-1}, 1608 cm^{-1} due to unsaturation, and at 1560 cm^{-1} , 1504 cm^{-1} ,835 cm^{-1} due to aromatic ring.

Thus, the characteristic IR absorption peaks were observed in the spectra of both pure drug and the dispersion of drug in PGS-PVP co-processed excipient in each case indicating no interaction between the new co-processed excipient and the three drugs included in the study.

CONCLUSION: PGS-PVP co-processed excipient prepared by gelatinizing potato starch (49 parts) in the presence of PVP (1 part) is a crystalline, discrete and free flowing powder. It is insoluble in water and aqueous fluids of pH 1.2, 4.5 and 7.4 and in several organic solvents. It exhibited high swelling (284%) in water. PGS-PVP co-processed excipient has excellent flow properties alone and as blends with selected drugs it exhibited excellent to good flow properties.

Tablets of (i) sulphamethoxazole (ii) paracetamol and (iii) aceclofenac prepared by direct compression method employing PGS-PVP co-processed excipient as DCV were of good quality with regard to drug content, hardness, friability and disintegration time. All the tablets formulated disintegrating rapidly within 3.5 min.

With all the three drugs, the tablets prepared gave rapid dissolution of the contained drug, 100 % within 20 min and fulfilled the official (IP/USP) dissolution rate test specification prescribed in each case. FTIR spectra indicated no interaction between PGS-PVP co-processed excipient and the three drugs included in the study.

Thus, PGS-PVP co-processed excipient developed in this study was found to be a promising directly compressible vehicle for the preparation of tablets.

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